Rheumatology Advance Access published October 27, 2015



Original article

doi:10.1093/rheumatology/kev373

# Eligibility for clinical trials in primary Sjögren's syndrome: lessons from the UK Primary Sjögren's Syndrome Registry

**Clare Oni[1], Sheryl Mitchell[2], Katherine James[3], Wan-Fai Ng[2,4], Bridget Griffiths[2], Victoria Hindmarsh[2], Elizabeth Price[5], Colin T. Pease[6,7], Paul Emery[6,7], Peter Lanyon[8], Adrian Jones[8], Michele Bombardieri[9], Nurhan Sutcliffe[9], Costantino Pitzalis[9], John Hunter[10], Monica Gupta[10], John McLaren[11], Annie Cooper[12], Marian Regan[13], Ian Giles[14], David Isenberg[14], Vadivelu Saravanan[15], David Coady[16], Bhaskar Dasgupta[17], Neil McHugh[18], Steven Young-Min[19], Robert Moots[20], Nagui Gendi[21], Mohammed Akil[22], Francesca Barone[23], Ben Fisher[23], Saaeha Rauz[23], Andrea Richards[24], Simon J. Bowman[1] on Behalf of the UK Primary Sjögren's Syndrome Registry***

## Abstract

**Objective:** To identify numbers of participants in the UK Primary Sjögren's Syndrome Registry (UKPSSR) who would fulfil eligibility criteria for previous/current or potential clinical trials in primary SS (pSS) in order to optimize recruitment.

**Methods:** We did a retrospective analysis of UKPSSR cohort data of 688 participants who had pSS with evaluable data.

**Results:** In relation to previous/current trials, 75.2% fulfilled eligibility for the Belimumab in Subjects with Primary Sjögren's Syndrome study (Belimumab), 41.4% fulfilled eligibility for the Trial of Remicade in primary Sjögren's syndrome study (Infliximab), 35.4% for the Efficacy of Tocilizumab in Primary Sjögren's Syndrome study (Tocilizumab), 31.6% for the Tolerance and Efficacy of Rituximab in Sjögren's Disease study (Rituximab), 26.9% for the Trial of anti-B-cell therapy in pSS study (Rituximab) and 26.6% for the Efficacy and Safety of Abatacept in Patients With Primary Sjögren's Syndrome study (Abatacept). If recent measures of outcome, such as the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score $\geqslant 5$ (measure of patient symptoms) and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score $\geqslant 5$ (measure of systemic disease activity) are incorporated into a study design, with requirements for an unstimulated salivary flow $>0$ and anti-Ro positivity, then the pool of eligible participants is reduced to 14.3%.

[1]Rheumatology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, [2]Rheumatology Department, Newcastle upon Tyne Hospitals NHS Foundation Trust, [3]Interdisciplinary Computing and Complex BioSystems Research Group, School of Computing Science, Newcastle University, Newcastle, [4]Musculoskeletal Research Group, Institute of Cellular Medicine & Newcastle NIHR Biomedical Research Centre for Ageing and Chronic Diseases, Newcastle University, Newcastle upon Tyne, [5]Rheumatology Department, Great Western Hospitals NHS Foundation Trust, Swindon, [6]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, [7]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, [8]Rheumatology Department, Nottingham University Hospital, Nottingham, [9]Department of Experimental Medicine and Rheumatology, Barts and the London NHS Trust and Barts and the London School of Medicine and Dentistry, London, [10]Rheumatology Department, Gartnavel General Hospital, Glasgow, [11]Rheumatology Department, NHS Fife, Whyteman's Brae Hospital, Kirkcaldy, [12]Rheumatology Department, Royal Hampshire County Hospital, Winchester, [13]Rheumatology Department, Royal Derby Hospital, Derby, [14]Rheumatology Department, University College London Hospitals NHS Foundation Trust, London, [15]Rheumatology Department, Queen Elizabeth Hospital, Gateshead, [16]Rheumatology Department, Sunderland Royal Hospital, Sunderland, [17]Rheumatology Department, Southend University Hospital, Southend, [18]Rheumatology Department, Royal National Hospital for Rheumatic Diseases, Bath, [19]Rheumatology Department, Portsmouth Hospitals NHS Trust, Portsmouth, [20]Rheumatology Department, Aintree University Hospitals, Liverpool, [21]Rheumatology Department, Basildon Hospital, Basildon, [22]Rheumatology Department, Royal Hallamshire Hospital, Sheffield, [23]Centre for Translational Inflammation Research, University of Birmingham, Birmingham and [24]Department of Oral Medicine, Birmingham Dental Hospital, Birmingham, UK

Submitted 18 May 2015; revised version accepted 10 September 2015

Correspondence to: Simon J. Bowman, Rheumatology Department, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK. E-mail: simon.bowman@uhb.nhs.uk

*For other collaborators in the UK Primary Sjögren's Syndrome Registry, see Acknowledgements section.

**Conclusion:** The UKPSSR identified a number of options for trial design, including selection on ESSDAI $\geqslant 5$, ESSPRI $\geqslant 5$ and serological and other parameters.

**Key words:** Sjögren's, clinical trial, eligibility, registry.

**Rheumatology key messages**

- This paper provides detailed information on disease phenotype in a large cohort of Sjögren's patients.
- This paper presents strategies to design clinical trial eligibility criteria in primary SS to optimize recruitment.

## Introduction

Primary SS (pSS) is an autoimmune rheumatic disease characterized by inflammation of the secretory glands leading to reduced/absent saliva and tear production [1]. It typically affects women in their middle years. As well as glandular features, fatigue and joint pains are the commonest symptoms reported by 70–80% of patients and a major cause of reduced health-related quality of life in pSS [2].

In total, 60–70% of patients with pSS have autoantibodies against the Ro +/– La antigens, and these patients are at risk of developing systemic complications such as salivary gland swelling, peripheral neuropathy, interstitial lung disease, arthritis and skin vasculitis [3]. A subset of pSS patients (circa 25%) with histological evidence of germinal centre formation on minor labial salivary gland biopsy, often with systemic disease, particularly salivary gland swelling, hypergammaglobulinaemia, low complement levels and salivary gland germinal centres, are at particular risk of developing mucosa-associated lymphoid tissue B–cell lymphoma [4].

Therapy for pSS is principally symptomatic using artificial tears and saliva replacement. Pilocarpine can be used to stimulate residual saliva production. HCQ and/or low dose prednisolone are often used to treat fatigue and arthralgia and conventional immunosuppressants for patients with multisystem involvement. None of these conventional therapies are of proven effectiveness for Sjögren's-specific features, and as a consequence there is a major unmet need for novel therapies.

In recent years, there has been considerable interest in targeted therapy of pSS using biologic therapies [5]. A trial of anti-TNF therapy (Trial of Remicade (infliximab) in pSS (TRIPSS)) did not, however, demonstrate benefit [6]. Rituximab, an anti-B-cell agent, however, has been effective in combination with conventional chemotherapy in treating B-cell lymphoma in pSS [7]. Since B-cell hyperactivity is commonly seen in pSS, Rituximab is a logical choice to trial in patients with pSS without lymphoma and has been evaluated for treating fatigue and other disease features in a number of open-label studies and case series [8]. Two initial pilot randomized controlled studies (RCTs) demonstrated benefit in fatigue and global health and in improving salivary flow and extraglandular features [9, 10]. Subsequently, there have been two larger clinical trials, one in France (Tolerance and Efficacy of Rituximab in Sjögren's Disease (TEARS)) [11], whose results have been published, and one currently taking place in the UK (Trial of anti-B-cell therapy in pSS (TRACTISS)) [12]. The TEARS study did not meet its primary end point, but did demonstrate improvements in fatigue from 6 weeks and dryness from 16 weeks.

An open-label study of 30 patients who received Belimumab has recently been reported (Efficacy and Safety of Belimumab in Subjects with Primary Sjögren's Syndrome (BELISS)) [13], and RCTs of Abatacept (NCT02067910) and of Tocilizumab (NCT01782235) are ongoing (https://www.clinicaltrials.gov).

One challenge in conducting trials of biologic therapies in pSS is determining eligibility and outcome criteria. A symptom questionnaire, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) [14], has been devised to measure dryness, fatigue and pain symptoms, and the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) to quantify systemic disease activity [15]. Data has been published identifying the thresholds for an unsatisfactory level of patient symptoms (ESSPRI $\geqslant 5$) and minimal clinically important improvement (MCII) of 1 point or 15% and of moderate systemic disease activity (ESSDAI $\geqslant 5$), severe systemic disease activity (ESSDAI $\geqslant 14$) and MCII of three points [16]. Initial clinical trial data has suggested that both ESSPRI and ESSDAI are sensitive to change [17, 18].

Given the heterogeneity of the patients, it can be a challenge to determine eligibility criteria that balance a sufficient level of disease activity/severity, as discussed in the above papers, or other patient stratification requirements to determine a meaningful clinical improvement, against the need for sufficiently broad entry criteria to facilitate recruitment as this is a significant potential barrier to successful trial completion [19].

This paper addresses the recruitment component of this equation. In order to do so we have interrogated the UK Primary Sjögren's Syndrome Registry, a cohort of around 700 patients representing clinical practice and recruited from a combination of district general and teaching hospitals in the UK [20]. In broad terms, the UK Primary Sjögren's Syndrome Registry (UKPSSR) represents the population from which patients would be recruited to clinical trials in the UK (and indeed has been for the TRACTISS Study [12]) and is therefore particularly suitable for this analysis. We evaluated available patient data in the UKPSSR against major eligibility criteria for the above studies, as well as considering the effect of other combinations of eligibility criteria that may reflect trial design in the future.

## Methods

### Participants

Recruitment to the UKPSSR started in August 2009. Data was available from 688 participants on 24 June 2013, when the data was downloaded for this analysis. Missing data is indicated in the text, with n = 688 used as the default denominator unless indicated. All participants fulfilled the American–European Consensus Group (AECG) classification criteria for primary Sjögren's Syndrome [21]. The UKPSSR is an human tissue act research database and tissue bank. National Health Service (NHS) Research Ethics Committee approval was obtained from National Research Ethics Service (NRES) Committee North West Haydock for the UKPSSR, to support a wide range of research projects in primary Sjogren's syndrome, including this analysis. All patients provided written informed consent for the UKPSSR.

The following parameters were evaluated: age, sex, current medication, ESSPRI and components (dryness, fatigue and pain), patient global assessment (assessed by the EQ5D visual analogue scale (VAS)), ESSDAI and components, Sjögren's Syndrome Damage Index (SSDI) [22], anti-Ro/La antibody status, unstimulated salivary flow rate (usf), disease duration from diagnosis (years), time from symptom onset (years), IgG and C3 and C4 levels, fibromyalgia and comorbidities. For the purposes of this study, a score of 5/10 on a Likert scale was taken to be equivalent to 50/100 on a VAS.

### Trial eligibility criteria evaluated

The UKPSSR data was evaluated against the major eligibility components of the following trials (see also the above Introduction section), approximated where necessary to reflect the data available. Trial of Remicade in primary Sjögren's syndrome (TRIPPS) [6]: AECG+, >50 mm out of 100 VAS of 2 out of 3 of the ESSPRI components (fatigue, pain and dryness), no immunosuppressive medication or pilocarpine (HCQ and prednisolone ⩽15 mg/day allowed). TEARS [11]: AECG+, active disease defined as ⩾50 mm out of 100 VAS of 2 out of 4 of the ESSPRI components and patient global assessment, disease symptom onset within 10 years and one biologic feature (autoantibodies; anti-Ro, rheumatoid factor (RF), cryoglobulinaemia, low complement C3 or C4, raised immunoglobulins, or B2-microglobulin) or at least one systemic feature or current parotid gland enlargement (broadly comprising the ESSDAI components used for this analysis), no immunosuppressive medication for 4 weeks (but stable dose HCQ, methotrexate, pilocarpine, prednisolone allowed). TRACTISS [12]: AECG+, anti-Ro+, ⩾5/10 fatigue and oral dryness (ESSPRI global dryness used instead for this evaluation) on a Likert scale. If more than 10 years since disease onset, at least one biologic feature (broadly comprising ESSDAI components), usf rate >0, stable dose of corticosteroid therapy, other immunosuppressant medication and/or pilocarpine allowed. BELISS [13]: AECG+, anti-Ro/La+, ⩾1 systemic feature (taken in this study to be at least one positive clinical ESSDAI domain score), or, one objective oral/ocular dryness feature + raised IgG or low C4 (or raised B2 microglobulin) or monoclonal gammopathy/cryoglobinopathy (taken as a positive ESSDAI biological domain score), or, disease duration < 5 years and all three ESSPRI domain scores >5. Efficacy and Safety of Abatacept in patients with Primary Sjögren's Syndrome (ASAPIII) NCT02067910: AECG+, ESSDAI ⩾5, disease duration ⩽ 7 years, no immunosuppressive medication or pilocarpine for 4 weeks, a stimulated salivary flow (ssf) exclusion – for the purpose of this paper considered with and without an additional usf = 0 exclusion. Efficacy of Tocilizumab in Primary Sjögren's Syndrome (ETAP) NCT01782235: AECG+, anti-Ro/La+, ESSDAI ⩾5, azathioprine and MMF excluded, also new or dose change in other medications within 2–8 weeks (consider with or without additional pilocarpine, prednisolone, disease-modifying anti-rheumatic drug medication exclusions). Potential study designs: AECG+, anti-Ro+, ESSPRI ⩾5, ESSDAI ⩾5/7/11/14, usf rate >0, disease duration since diagnosis <5/<10 years/any, stable therapy allowed/stopped.

### Statistical analysis

Data was analysed using Microsoft Excel for basic descriptive statistics, Statistical Package for the Social Sciences (SPSS) for most comparative analyses and the Social Science Statistics website (http://www.socscistatistics.com/) for $Chi^2$ analyses. For comparison of distributions between groups, the Mann–Whitney *U* test (independent samples) was used. $Chi^2$ was used for comparison of discontinuous variables between groups. Spearman's test was used for correlation analysis. $P < 0.05$ was taken as significant throughout.

## Results

The frequencies of participant characteristics are set out in Table 1. The frequencies of participants with individual ESSDAI domain scores of 1 or more as well as of participants with positive SSDI damage item/domain scores can be found in supplementary Table S1, available at *Rheumatology* Online.

Table 2 presents the frequencies of eligible participants according to the different trial eligibility criteria. BELISS was most permissive at 75.2%, with three different ways to meet eligibility criteria. TEARS and TRIPSS were next, with almost half of the cohort potentially eligible (46.3% and 41.4%, respectively), whereas the ETAP, ASAPIII and TRACTISS protocols would allow between a quarter and just over a third of the patients potentially to participate (35.4%, 26.6% and 26.9%, respectively). Although data is also presented on the lower numbers when excluding specified medications, these are slightly artificial in that many patients who wish to participate would likely be able to come off these medications to meet eligibility criteria.

### ESSPRI and ESSDAI thresholds and other core parameters

Table 3 presents data for a potential study that varies a number of key parameters, including anti-Ro+/– as the

**Table 1** Database patient demographics, n = 688

| | |
|---|---|
| Age, years, mean (S.D.) | 58.5 (12.5) |
| % patients <18 | 0 |
| % patients >80 | 1.7 |
| Sex, M %; F % | 5.4; 94.6 |
| Current medications, % | |
| HCQ | 38.5 |
| CYC | 0.15 |
| AZA | 3.5 |
| Mycophenylate | 1.5 |
| MTX | 2.6 |
| Rituximab[a] | 0.9 |
| Oral corticosteroids | 10.9 |
| Pilocarpine | 7.5 |
| HCQor oral corticosteroid | 46.8 |
| DMARD (AZA, MTX, SZP, LEF, CYA, MMF, TAC) | 8.7 |
| Pilocarpine or a DMARD | 15.4 |
| Rituximab/CYC/IVIG/Chlorambucil/ chemotherapy/other | 1.7 |
| ESSPRI | |
| Mean dryness score (S.D.) | 6.0 (2.6) |
| Mean fatigue score (S.D.) | 5.5 (2.7) |
| Mean pain score | 4.5 (3.0) |
| Mean ESSPRI score | 5.3 (2.2) |
| Dryness score ⩾5, % | 71.5 |
| Fatigue score ⩾5, % | 64.3 |
| Pain score ⩾5, % | 51.5 |
| Mean ESSPRI score ⩾5, % | 60.2 |
| 2/3 ESSPRI ⩾5, % | 65.1 |
| Fatigue score ⩾5 and dryness score ⩾5, % | 54.7 |
| ESSDAI | |
| Mean ESSDAI | 4.8 (4.9) |
| ESSDAI =0, % | 17.3% |
| ESSDAI ⩾5, % | 41.7% |
| ESSDAI ⩾7, % | 28.9% |
| ESSDAI ⩾9, % | 17.3% |
| ESSDAI ⩾11, % | 11.8% |
| ESSDAI ⩾14, % | 5.1% |
| ESSPRI ⩾5 and ESSDAI ⩾5, % | 27.2% |
| SSDI oral score, mean (S.D.) | 1.59 (1.14) |
| SSDI ocular score, mean (S.D.) | 0.58 (0.73) |
| SSDI systemic score, mean (S.D.) | 0.41 (0.73) |
| Mean EQ5D global score | 60.3 |
| Anti-Ro +, % | 87.1 |
| Anti-La +, % | 70.8 |
| Anti-La + but anti-Ro−, % | 0.6 |
| Fibromyalgia, % | 9.0 |
| Either anti-Ro+/anti-La+/high IgG/lowC3/lowC4, % | 89.1 |
| usfrate >0mls/15 min, % | 63.1 |
| Unstimulated flow rate > 1.5mls/15 min, % | 19.8 |
| Schirmer I test (average of both eyes) > 0mm/5 min, % | 77.8 |
| Schirmer I test (average of both eyes) > 5mm/5 min, % | 36.8 |
| Disease symptom duration, mean (S.D.), years | 6.7 (6.0) |
| Disease duration <5 years, % | 50.2 |
| Disease duration <10 years, % | 76.1 |
| Low C3, % | 6.7 |
| Low C4, % | 21.2 |
| Lymphoma, % | 6.8 |
| Other malignancy, % | 5.5 |
| Mean IgG level | 16.5 |
| IgG >16, % | 44.3 |

[a]No patients on etanercept or infliximab. ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; SZP: Sulfasalazine EN; TAC: Tacrolimus; CYA: Ciclosporin.

**Table 2** Number of patients from the database eligible for the following trials, total n = 681

| | N (%) |
|---|---|
| ABATACEPT (ASAPIII) | 181 (26.6) |
| no medications allowed | 75 (11.0) |
| usf =0 | 118 (17.3) |
| no medications allowed and usf =0 | 46 (6.8) |
| BELIMUMAB (BELISS) | 512 (75.2) |
| RITUXIMAB (TEARS (FRANCE)) | 315 (46.3) |
| INFLIXIMAB (TRIPSS) | 282 (41.4) |
| If pilocarpine, MTX, AZA or MMF allowed | 339 (49.8) |
| RITUXIMAB (TRACTISS (UK)) | 183 (26.9) |
| TOCILIZUMAB (ETAP) | 241 (35.4) |
| no medications allowed | 99 (14.5) |

ASAPIII: Efficacy and Safety of Abatacept in Patients With Primary Sjögren's Syndrome; ETAP: Efficacy of Tocilizumab in Primary Sjögren's Syndrome; BELISS: Efficacy and Safety of Belimumab in Subjects With Primary Sjögren's Syndrome; TEARS: Tolerance and Efficacy of Rituximab in Sjögren's Syndrome; TRACTISS: Trial of Anti-B-Cell Therapy in primary Sjögren's Syndrome; TRIPSS: Trial of Remicade in Primary Sjögren's Syndrome; usf: unstimulated salivary flow rate; N: number.

key serological item, usf >0 or =0, an ESSDAI score meeting the cut-off for moderate disease of ⩾5 [14], or higher thresholds and an ESSPRI symptom score ⩾5 recommended as the minimum threshold for clinical trials [14] or with 2/3 items ⩾5, and by different maximum disease duration cut-offs. In total, 14.4% of the participants meet these potential criteria based on anti-Ro+, ESSPRI ⩾5, ESSDAI ⩾5 and usf >0. If the serological component of the eligibility criteria (i.e. a requirement to be anti-Ro+) is not obligatory, then 16.4% of participants meet the criteria (Table 3). If neither pilocarpine, nor DMARD therapy is allowed, then the eligible percentage falls to 9.2%. If the ESSDAI threshold is increased above 5 and/or disease duration reduced below 5 years, then the eligible numbers falls substantially. Alternatively, if only ESSPRI ⩾5 and ESSDAI ⩾5 alone are mandatory, then 27.2% of participants become eligible.

Table 4 sets out data using an alternative approach in which patients are selected according to only one parameter (ESSPRI ⩾5, ESSDAI ⩾5, anti-Ro + or usf >0) and to examine whether there is enrichment for any of the other parameters in the group positive for the original parameter. There is modest mutual enrichment for ESSPRI ⩾5 and ESSDAI ⩾5 (P = 0.01), and there is a correlation between the two scores (n = 678, Spearman correlation rho = 0.142, P < 0.001. Anti-Ro− patients are more likely to have an usf >0 and vice versa (P = 0.04).

## Serology

In total, 87.1% of the cohort are anti-Ro + (missing n = 4). If this is extended to allow alternative serological features (low complement levels or raised IgG levels), this increases to 89.1%. The UKPSSR does not include

**Table 3** Number of patients from the database eligible for a theoretical study

| Stable therapy allowed Ro+, ESSPRI ⩾5, usf>0 | Disease Duration, N (%) | | |
|---|---|---|---|
| | Any | <10 years | <5 years |
| ESSDAI ⩾5 | 99 (14.4) | 79 (11.5) | 49 (7.1) |
| ESSDAI ⩾7 | 66 (9.6) | 57 (8.3) | 35 (5.1) |
| ESSDAI ⩾9 | 39 (5.7) | 32 (4.7) | 18 (2.6) |
| ESSDAI ⩾11 | 26 (3.8) | 20 (2.9) | 10 (1.5) |
| ESSDAI ⩾14 | 12 (1.7) | 11 (1.6) | 7 (1.0) |
| Ro+, ESSDAI ⩾5, usf>0 ESSPRI 2/3⩾5[a] | 111 (16.1) | 85 (12.4) | 51 (7.4) |
| Ro+, ESSDAI ⩾5, usf>0, ESSPRI any | 151 (21.9) | 125 (18.2) | 81 (11.8) |
| ESSDAI ⩾5, usf>0, ESSPRI⩾5 with Ro+/– | 113 (16.4) | 84 (12.2) | 54 (7.8) |
| ESSDAI ⩾5, ESSPRI⩾5, Ro+/–, usf⩾0 | 187 (27.2) | 134 (19.5) | 85 (12.4) |
| Ro+, ESSPRI⩾5, ESSDAI ⩾5, usf > 0, no pilocarpine | 90 (13.1) | 73 (10.6) | 46 (6.7) |
| Ro+, ESSDAI ⩾5, usf>0, ESSPRI⩾5, no pilocarpine or DMARD | 82 (11.9) | 63 (9.2) | 33 (4.8) |

Data presented here according to ESSPRI >5 ([a]or 2/3 components >5 where indicated), ESSDAI score, disease duration and, where indicated, whether Ro+/–, whether usf >0 or not and/or whether current pilocarpine or DMARD therapy is allowable. DMARDs are AZA, MTX, SZP, LEF, CYA, MMF, TAC. ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; usf: unstimulated salivary flow rate; SZP: Sulfasalazine EN; TAC: Tacrolimus; CYA: Ciclosporin.

**Table 4** Numbers of participants per category based on selecting by the parameter listed in the left-hand column

| Selected parameter | Subgrouped parameter | | | |
|---|---|---|---|---|
| | ESSPRI ⩾5 | ESSDAI ⩾5 | Anti-Ro+ | Usf >0 |
| ESSPRI ⩾5; n = 408–409 | — | 186/408 (45.6%) | 352/408 (86.3%) | 249/409 (60.9%) |
| ESSPRI <5; n = 267–270 | — | 94/270 (34.8%) | 241/267 (90.3%) | 176/270 (65.2%) |
| Chi$^2$ | — | P = 0.01[a] | P = 0.12 | P = 0.26 |
| ESSDAI ⩾5; n = 280–287 | 186/280 (66.4%) | — | 256/287 (89.2%) | 177/287 (61.7%) |
| ESSDAI <5; n = 396–400 | 222/398 (55.8%) | — | 339/396 (85.6%) | 257/400 (64.3%) |
| Chi$^2$ | P = 0.01[a] | — | P = 0.17 | P = 0.49 |
| Anti-Ro+; n = 593–596 | 352/593 (59.4%) | 256/595 (43.0%) | — | 366/596 (61.4%) |
| Anti-Ro–; n = 82–88 | 56/82 (68.3%) | 31/88 (35.2%) | — | 64/88 (72.7%) |
| Chi$^2$ | P = 0.12 | P = 0.17 | — | P = 0.04[a] |
| Usf >0; n = 425–434 | 249/425 (58.6%) | 177/434 (40.8%) | 366/430 (85.1%) | — |
| Usf =0; n = 253–254 | 160/254 (63.0%) | 110/253 (43.5%) | 230/254 (90.6%) | — |
| Chi$^2$ | P = 0.26 | P = 0.49 | P = 0.04[a] | — |

(ESSPRI >5 or <5; ESSDAI >5 or <5; anti-Ro+/-; usf >0 or =0) and then subgrouping by each of the parameters individually. Missing data: ESSPRI n = 9, ESSDAI n = 1, anti-Ro n = 4, usf n = 0. [a]Significant at P = 0.05. ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

sufficiently detailed information about RF and ANA, but in the Sjögren's International Collaborative Clinical Alliance (SICCA) cohort, circa 1% of participants were anti-Ro–, anti-La-, ANA ⩾320 + and RF + (Shiboski C & Shiboski S, personal communication), which if applied to the UKPSSR, would bring the total numbers of participants with a relevant serological abnormality to just over 90%.

In this present study of the UKPSSR cohort, the mean ESSPRI (missing n = 9) among 593 anti-Ro + participants with complete data for both ESSPRI and anti-Ro was 5.25 (S.D.= 2.23) (median = 5.33, interquartile range 3.67–7) and among 82 anti-Ro– participants with complete data was 5.91 (S.D.= 2.10) (median = 6.33, interquartile range 4.33–7.33) (P = 0.011; Mann–Whitney *U* test). The mean ESSDAI (missing n = 1) among 595 Ro + participants with complete data was 5.07 (S.D.= 5.12) (median= 4, interquartile range 1–7) and among 88 Ro– participants was 3.31 (S.D.= 2.95) (median = 3, interquartile range 0–5) (P = 0.006; Mann–Whitney *U* test).

### Unstimulated salivary flow of zero and disease duration

In this study, 434/688 (63.1%) of participants had an usf > 0. The mean of the ESSPRI dryness Likert score was lower at 5.53 (S.D.= 2.53) (median = 6, interquartile range 4–8) in 426 participants, with an usf > 0, compared with

6.78 (S.D.= 2.43) (median = 7, interquartile range 5–9) among 254 participants with an usf of zero ($P < 0.001$; Mann–Whitney *U* test) (missing n = 8).

The mean ESSPRI score overall (which also includes fatigue and pain), however, was similar at 5.21 (S.D.= 2.22) (median = 5.33, interquartile range 3.67–7) among 425 participants with an usf > 0, compared with 5.52 (S.D.= 2.21) (median = 5.67, interquartile range 4–7.08) among 254 with an usf =0 (Mean ESSPRI missing n = 9) (P = 0.129; Mann–Whitney *U* test).

The mean ESSDAI score was also similar at 4.65 (S.D.= 4.74) (median = 3, interquartile range 1.75–7) among 434 participants with an usf > 0, compared with 5.11 (S.D.= 5.22) (median = 4, interquartile range 1–7) among 253 participants with an usf =0 (P = 0.41; Mann–Whitney *U* test). The mean disease duration (missing n = 29) was slightly lower at 6.27 years (S.D.= 5.81) (median = 4.67, interquartile range 1.67–8.67) among 415 participants with an usf >0 compared with 7.43 (S.D.= 6.12) (median = 5.92, interquartile range 2.44–11.46) among 244 participants with an usf of zero (P = 0.01; Mann–Whitney *U* test).

Examining this the other way round, common eligibility thresholds that can be arbitrarily proposed for maximum disease duration (from formal medical diagnosis) are <5 years or <10 years. The rationale is that patients with earlier disease arguably have more activity and less damage. Table 5 sets out the frequencies of patients with an ESSPRI ⩾5, ESSDAI ⩾5, anti-Ro + and usf >0 in these three groups. The only significant difference is that patients with a disease duration of 10 years or more have a greater likelihood of an usf =0 ($Chi^2 = 9.99$, P = 0.007) and, in keeping with this disease, duration correlates inversely with usf (Spearman correlation rho = −0.108, P = 0.006).

## Discussion

There is a huge unmet need for novel therapies for pSS [23]. A number of clinical trials of such therapies are now underway or planned [5]. Designing clinical trials in the absence of proven therapy, however, is a challenge. There has been significant progress on developing outcome tools for pSS such as the ESSPRI [14] and ESSDAI [15] and the definition of MCII and the patient-acceptable symptom state (PASS) [16]. This study interrogates the UKPSSR in order to address the question of how various eligibility criteria affect potential recruitment numbers.

Anti-Ro and anti-La antibodies are the key antibodies associated with pSS. In most cohorts, circa 70–80% of patients are positive for anti-Ro/La [3, 24]. The UKPSSR has a higher percentage at 87.7%. This most likely reflects the fact that this pragmatic study recruits participants from around the UK, where the majority of units do not have access to minor labial salivary gland biopsy, thus requiring the presence of these antibodies to fulfil AECG criteria, leading to a bias in recruitment towards anti-Ro + participants [20]. The rationale for only including participants with anti-Ro + (and/or other serological positivity) is that this group is more homogeneous and likely to represent those with a clear-cut diagnosis, those having underlying immune-based disease, and those with systemic disease, although in this study, the percentage of anti-Ro + patients with an ESSDAI ⩾5 did not differ statistically from the percentage of patients who were anti-Ro– (43.0% versus 35.2% $Chi^2$ P = 0.17). Including patients lacking anti-Ro or anti-La antibodies, but who are ANA + or RF + or have raised immunoglobulins or low complement levels, is an alternative potential strategy to broaden the serology-positive group. This current study was not able to evaluate ANA and RF directly, but in other previously reported cohorts, ANA positivity was at 80–90% of participants [3, 24], although this is dependent on the definition of ANA positivity. RF positivity was less common [3, 24].

With regard to glandular function, particularly salivary function, the goal is to identify participants who maintain sufficient residual function in order to respond to therapy, and in whom the mechanism of reduced saliva function is due to inflammation rather than atrophy or fibrosis. Labial gland biopsy and/or salivary gland ultrasound may be helpful in clarifying the level of structural changes in the glands [25, 26]. ssf appears to reflect inflammation more closely than usf [25]. ssf can be measured using several techniques (e.g. using citric acid solution, by rolling a metallic or glass ball, or by chewing on paraffin wax), and a ssf of zero is an indicator that there is glandular damage that may not respond to therapy. An usf, however, can be easily measured during a routine clinic, and may therefore lend itself more easily to initial screening of patients with potentially absent ssf.

**Table 5** Numbers of participants grouped by disease duration (<5 years, 5 to <10 years and >10 years)

| | <5 years (n = 327–330) | 5 to <10 years (n = 170–171) | ⩾10 years (n = 157–158) | $Chi^2$ between groups |
|---|---|---|---|---|
| ESSPRI ⩾5 | 185/330 (56.1%) | 103/171 (60.2%) | 103/158 (65.2%) | $Chi^2 = 3.77$, P = 0.15 |
| ESSDAI ⩾5 | 139/330 (42.1%) | 71/171 (41.5%) | 65/157 (41.4%) | $Chi^2 = 0.03$, P = 0.99 |
| Anti-Ro+ | 291/328 (88.7%) | 158/170 (92.9%) | 139/158 (88.0%) | $Chi^2 = 2.76$, P = 0.25 |
| Usf >0[a] | 216/330 (65.5%) | 116/171 (67.8%) | 83/158 (52.5%) | $Chi^2 = 9.99$, P = 0.007 |

Data was available from 659 particpants (missing disease duration data n = 29) and is set out for ESSPRI, ESSDAI, anti-Ro antibody status and usf. Numbers with available data are indicated in the Table. [a]Disease duration correlated inversely with usf (n = 659, Spearman correlation rho = −0.108, P = 0.006). ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index.

Disease duration is also potentially relevant. The assumption is made, based on the rheumatoid arthritis model [27], that earlier disease is more likely to be due to active inflammation, and later disease is more likely to reflect damage (or at least a lower amenability to immunomodulation). In this study, there was a statistically significant (but modest) inverse correlation between disease duration and usf (Spearman correlation rho = –0.108, P = 0.006). There was a statistically significantly lower proportion of participants with a usf >0 in participants with a disease duration of <10 years compared with those with a disease duration of 10 or more years (66.3% compared with 52.5% ($Chi^2 = 9.72$, P = 0.002)). Although these differences are statistically significant, this is largely due to the big sample size, and the clinical effect size is small. Nevertheless, this data would potentially support a cut-off of <10 years for trial entry. Over half of the participants with a disease duration of 10 years or more still, however, have a usf >0, so an alternative option is to set the eligibility criteria around salivary flow directly rather than disease duration.

With regard to patient symptoms and systemic disease, the ESSPRI and ESSDAI are now regarded as the gold-standard measures, and recent data identifies an ESSDAI threshold score of 5 or more to identify moderate or severe systemic disease activity [14]. For the ESSPRI, a score of 5 or more is above the PASS. In total, 59.6% of participants in the UKPSSR had an ESSPRI of 5 or more, and 41.7% had an ESSDAI of 5 or more. There is no higher threshold for ESSPRI, but an ESSDAI of 14 or more (5.1% of participants) is defined as severe systemic disease. What is clear from these percentages is that choosing an ESSDAI eligibility threshold above 5 is likely to be challenging from the perspective of recruitment due to the rapid fall-off in numbers of eligible participants as the ESSDAI threshold rises above 5. An increase in the eligibility threshold from an ESSDAI $\geqslant 5$ to an ESSDAI $\geqslant 7$, for example, means a drop in potentially eligible participants from 41.7% to 28.9% of the cohort. At an ESSDAI of 5–7, in those patients where a raised IgG level is contributing two points to the total ESSDAI score through the biological domain (maximum domain score =2), this may need to be considered in terms of the clinical relevance of an improvement in the total ESSDAI score.

Recruiting participants with 2 out of 3 ESSPRI components with a score of 5 or more instead of a mean ESSPRI score of 5 or more generates a small increase in eligible participants from 59.6% to 65.1%. Arguably, this option increases complexity in assessing outcome, although it may helpfully link outcome to individual patient characteristics. Validation of the PASS and the minimal clinically MCII level has been performed on the total ESSPRI score not on a 2/3 component improvement, which may limit this option.

Although there are some statistical relationships between ESSPRI, ESSDAI, anti-Ro antibodies and usf (as set out in Table 4), again the rho values are modest, with none of them so striking as to offer a clear strategy for selecting one parameter so as to also enrich for another. Medication is a potential eligibility criterion. In total, 38.5% of UKPSSR participants were taking HCQ. Excluding patients on this medication, or requiring a lengthy period off this medication prior to recruitment (e.g. [mt]4 weeks), is likely to have an impact on recruitment. Pilocarpine, oral corticosteroids and DMARDs are each taken by 7.5–10.9% of participants, and while each of these might appear to be a relatively small number, cumulatively this becomes significant.

Evaluating the trials to date, TRIPPS selected essentially on ESSPRI alone, with modest restriction in medications. TEARS and TRACTISS add a requirement for anti-Ro + and a usf >0, and (as a consequence) eligibility falls to 31.6% and 26.9%, respectively. ETAP and ASAPIII focus on the ESSDAI and require an ESSDAI score of at least 5 (moderate systemic disease activity) with anti-Ro + required for ETAP. BELISS, which also includes anti-Ro+, offers an interesting way of maximizing recruitment by offering different routes to eligibility, including ESSDAI, ESSPRI or objective dryness. In a theoretical study that incorporates ESSDAI $\geqslant 5$, the percentage eligible reduces to 14.3%. If eligibility is based around ESSDAI $\geqslant 5$, without reference to ESSPRI (Ro+, usf >0), then 21.9% become eligible.

The JOQUER trial of HCQ versus placebo in pSS [28] offers an alternative approach, which is essentially to accept nearly all patients with pSS, subject only to some limitations around current and previous therapies. This has the benefit of optimizing recruitment, but is potentially more challenging in demonstrating efficacy, which (as discussed here) is also a major consideration, particularly for new expensive biologic therapies.

In terms of putting this all together as a general starting proposal for trial eligibility based around optimizing recruitment, the following could be considered, based on the UKPSSR Registry data: to require anti-Ro antibody positivity for trials requiring patient homogeneity, or, where this is less critical but where serological evidence of immune activity is still desirable, to offer serological criteria that are as broad as possible (but still requiring the AECG criteria for trial entry) e.g. potentially to allow any of Ro+, La+, ANA+, RF+, IgG >16, or low C3 or C4; for studies where residual glandular function is important, to exclude participants with a ssf =0 and to consider using usf as a means of pre-screening for suitable individuals in a routine clinic; allow stable medication for 4 weeks before the baseline visit wherever possible.

Disease duration does not appear to be an absolutely critical restriction, but <10 years from formal diagnosis could be considered (recognizing the limitations of this). Consider selecting either for ESSPRI $\geqslant 5$ or ESSDAI $\geqslant 5$ for outcome, whereas recruitment based on having both an ESSDAI $\geqslant 5$ as well as an ESSPRI $\geqslant 5$ may be challenging because it reduces the potential pool of participants by circa 60%. With a number of clinical trials taking place over the next few years, further clarification and refinement of these eligibility criteria will be likely as data from these further trials becomes available (in terms of setting criteria to optimize the likelihood of demonstrating improvement in the

outcome measures and also of balancing this against optimizing recruitment, as evaluated in this study).

## Acknowledgements

We thank the Medical Research Council (grant G0800629 to W.F.N., S.J.B., B.G.) for funding the UKPSSR. We also thank all the patients who participated in the study and the British Sjögren's Syndrome Association, the Newcastle National Institute for Health Research (NIHR) Biomedical Research Centre and the Sir Samuel Scott of Yews Trust for additional support. We also thank Dr Peter Nightingale for expert statistical advice. This study is a research output of the UKPSSR, which is funded by the Medical Research Council.

W.F.N., S.J.B. and B.G. are investigators of the UKPSSR. Other UKPSSR members include, in alphabetical order of their affiliation: Elalaine C Bacabac, Robert Moots (Aintree University Hospitals); Kuntal Chadravarty, Shamin Lamabadusuriya (Barking, Havering and Redbridge NHS Trust); Michele Bombardieri, Constantino Pitzalis, Nurhan Sutcliffe (Barts and the London NHS Trust); Rashidat Adeniba, Nagui Gendi (Basildon Hospital); John Hamburger, Jon Higham, Ana Poveda-Galego, Andrea Richards (Birmingham Dental Hospital); Joanne Logan, Diarmuid Mulherin (Cannock Chase Hospital); Jacqueline Andrews, Paul Emery, Alison McManus, Colin Pease (Chapel Allerton Hospital, Leeds); Alison Booth, Marian Regan (Derbyshire Royal Infirmary); Theodoros Dimitroulas, Lucy Kadiki, Daljit Kaur, George Kitas (Dudley Group of Hospitals NHS Foundation Trust); Mark Lloyd, Lisa Moore (Frimley Park Hospital); Esther Gordon, Cathy Lawson (Harrogate District Foundation Trust Hospital); Monica Gupta, John Hunter, Lesley Stirton (Gartnavel General Hospital, Glasgow); Gill Ortiz, Elizabeth Price (Great Western Hospital); Gavin Clunie, Sue Cuckow, Ginny Rose (Ipswich Hospital NHS Trust); Beverley Jones, Susan Knight, Deborah Symmons (Macclesfield District General Hospital & Arthritis Research UK Epidemiology Unit, Manchester); Andrew Carr, Marco Carrozzo, Suzanne Edgar, Francisco Figuereido, Heather Foggo, Colin Gillespie, Dennis Lendrem, Iain Macleod, Sheryl Mitchell, Jessica Tarn (Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University); Adrian Jones, Peter Lanyon, Alice Muir (Nottingham University Hospital); Paula White, Steven Young-Min (Portsmouth Hospitals NHS Trust); Susan Pugmire, Saravanan Vadivelu (Queen's Elizabeth Hospital, Gateshead); Annie Cooper, Marianne Watkins (Royal Hampshire County Hospital); Anne Field, Stephen Kaye, Patricia Medcalf, Devesh Mewar, Pamela Tomlinson, Debbie Whiteside (Royal Liverpool University Hospital); Julie James, Neil McHugh, John Pauling, Nike Olaitan (Royal National Hospital for Rheumatic Diseases); Mohammed Akil, Olivia Godia, Jayne McDermott (Royal Hallamshire Hospital, Sheffield); David Coady, Elizabeth Kidd, Lynne Palmer (Royal Sunderland Hospital); Bhaskar Dasgupta, Victoria Katsande, Pamela Long (Southend University Hospital); Usha Chandra, Kirsten MacKay (Torbay Hospital); Stefano Fedele, Ada Ferenkeh-Koroma, Ian Giles, David Isenberg, Helena Marconnell, Stephen Porter (University College Hospital & Eastman Dental Institute); Sue Brailsford (University Hospital Birmingham); Francesca Barone, Ben Fisher, Saaeha Rauz (University of Birmingham); Paul Allcoat, John McLaren (Whyteman's Brae Hospital, Kirkcaldy).

*Funding*: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

*Disclosure statement*: S.J.B has been on advisory boards, consultant to, received research support, regarding Sjogren's syndrome, from Cellgene, Glenmark, Glaxosmithkline (GSK), E Lilly, Medimmune, Novartis, Pfizer, Roche and UCB. B.D. is a consultant for clinical trial design for Roche, GSK, Servier, Merck and Mundipharma and has received a grant from Napp. I.G. is on advisory boards and received honoraria from Pfizer and UCB. B.F. has been on advisory boards and received honoraria from Medimmune, Takeda and Virtualscopics. F.B. has acted as a consultant for GSK, UCB, Medimmune and Glenmark. B.G. has served on advisory boards for Actelion, Pfizer and Roche. W.-F.N. has consulted for Pfizer, Sanofi, MedImmune and Takeda and received honoraria for speaking engagement for Roche, UCB, and Eisai. P.E. has received consultancy fees from Bristol Myers Squibb (BMS), Abbott, Pfizer, Merck Sharp and Dohme Ltd (MSD), Novartis, Roche and UCB and has received research grants paid to his employer from Abbott, BMS, Pfizer, MSD and Roche. All other authors have declared no conflicts of interest.

## Supplementary data

Supplementary data are available at *Rheumatology* Online.

## References

1 Jonsson R, Bowman SJ, Gordon TP. Sjogren's syndrome. In: Koopman WJ, Moreland LW, eds. Arthritis and allied conditions, 15th edn. Philadelphia, USA: Lippincott Williams & Wilkins, 2005: 1681–705.

2 Bowman SJ, Booth DA, Platts RG, UK Sjögren's Interest Group. Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. Rheumatology 2004;43:758–64.

3 Ramos-Casals M, Brito-Zero P, Solans R *et al*. Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology 2014;53:321–31.

4 Theander E, Vasaitis L, Baecklund E *et al*. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis 2011;70:1363–8.

5 Sada PR, Isenberg D, Ciurtin C. Biologic treatment in Sjögren's syndrome. Rheumatology 2015;54:219–30.

6 Mariette X, Ravaud P, Steinfeld S *et al*. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis Rheum 2004;50:1270–6.

7 Voulgarelis M, Giannouli S, Tzioufas AG, Moutsopoulos HM. Long term remission of Sjögren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Ann Rheum Dis 2006;65:1033–7.

8 Bowman S, Barone F. Biologic treatments in Sjogren's syndrome. Presse Med 2012;41:e495–509.

9 Dass S, Bowman SJ, Vital EM *et al*. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541–4.

10 Meijer JM, Meiners PM, Vissink A *et al*. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960–8.

11 Devauchelle-Pensec V, Mariette X, Jousse-Joulin S *et al*. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med 2014;160:233–42.

12 Brown S, Navarro Coy N, Pitzalis C *et al*. The TRACTISS protocol: a randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patients with primary Sjögren's Syndrome. BMC Musculoskelet Disord 2014;15:21.

13 Mariette X, Seror R, Quartuccio L *et al*. Efficacy and safety of belimumab in primary Sjogren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis 2015;74:526–31.

14 Seror R, Ravaud P, Mariette X *et al*. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. Ann Rheum Dis 2011;70:968–72.

15 Seror R, Ravaud P, Bowman SJ *et al*. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103–9.

16 Seror R, Bootsma H, Saraux A *et al*. Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis 2014 (in press); pii: annrheumdis-2014-206008. doi: 10.1136/annrheumdis-2014-206008. [Epub ahead of print].

17 Meiners PM, Arends S, Brouwer E *et al*. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297–302.

18 Moerman RV, Arends S, Meiners PM *et al*. EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial. Ann Rheum Dis 2014;73:472–4.

19 Bowman SJ, Macfarlane GJ, Arthritis Research Campaign Data Monitoring Committee. Successful patient recruitment in investigator-led clinical trials. Rheumatology 2007;46:1207–8.

20 Ng WF, Bowman SJ, Griffiths B, UKPSSR study group. United Kingdom Primary Sjögren's Syndrome Registry: a united effort to tackle an orphan rheumatic disease. Rheumatology 2011;50:32–9.

21 Vitali C, Bombardieri S, Jonsson R *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis 2002;61:554–8.

22 Barry RJ, Sutcliffe N, Isenberg DA *et al*. The Sjögren's Syndrome Damage Index—a damage index for use in clinical trials and observational studies in primary Sjögren's syndrome. Rheumatology 2008;47:1193–8.

23 Bowman SJ, St Pierre Y, Sutcliffe N *et al*. Estimating indirect costs in primary Sjögren's syndrome. J Rheumatol 2010;37:1010–5.

24 Baldini C, Pepe P, Quartuccio L *et al*. Primary Sjögren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. Rheumatology 2014;53:839–44.

25 Bookman AA, Shen H, Cook RJ *et al*. Whole stimulated salivary flow: correlation with the pathology of inflammation and damage in minor salivary gland biopsy specimens from patients with primary Sjögren's syndrome but not patients with sicca. Arthritis Rheum 2011;63:2014–20.

26 El Miedany YM, Ahmed I, Mourad HG *et al*. Quantitative ultrasonography and magnetic resonance imaging of the parotid gland: can they replace the histopathologic studies in patients with Sjögren's syndrome? Joint Bone Spine 2004;71:29–38.

27 Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol 2003;21:S154–7.

28 Gottenberg JE, Ravaud P, Puechal X *et al*. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA 2014;312:249–58.